# Mathematical Modeling of Liver Injury and Dysfunction After Acetaminophen Overdose: Early discrimination between survival and death

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**Abstract**

Acetaminophen is the leading cause of acute liver injury in the developed world. Timely administration of N-Acetylcysteine (N-Ac) prevents the progression of serious liver injury and disease, while failure to administer N-Ac within a critical time frame allows disease progression and in the most severe cases may result in liver failure or death. In this situation, liver transplantation may be the only life-saving measure. Thus, the outcome of an acetaminophen overdose depends upon the size of the overdose and the time to first administration of N-Ac. We developed a system of differential equations to describe acute liver injury due to acetaminophen overdose. The Model for Acetaminophen-induced Liver Damage (MALD) uses a patient's AST, ALT, and INR measurements on admission to estimate overdose amount, time elapsed since overdose, and outcome. The mathematical model was then tested on 53 patients from the University of Utah. With the addition of serum creatinine, eventual death was predicted with 100% sensitivity, 91% specificity, 67% PPV, and 100% NPV in this retrospective study. Using only initial AST, ALT, and INR measurements, the model accurately predicted subsequent laboratory values for the majority of individual patients. This is the first dynamical rather than statistical approach to determine poor prognosis in patients with life-threatening liver disease due to acetaminophen overdose. Conclusion: MALD provides a method to estimate overdose amount, time elapsed since overdose, and outcome from patient laboratory values commonly available on admission in cases of acute liver failure due to acetaminophen overdose and should be validated in multicentric prospective evaluation.



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**Keywords:** acute liver failure; mathematical modeling; MALD; paracetemol

## 1 Introduction

Acetaminophen (APAP: N-acetyl-para-aminophenol) is the leading cause of acute liver injury in the USA, accounting for some 56,000 emergency room visits, 26,000 hospital admissions and about 500 deaths annually [1]. APAP toxicity is caused by the formation, within hepatocytes, of N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive benoquinonamine [2,3]. Intracellular NAPQI initially binds to glutathione (GSH), and is safely eliminated [4,5]. Once GSH stores are depleted, residual free NAPQI reacts with cellular components and causes injury to APAP-metabolizing hepatocytes [6,7]. Early administration of the GSH precursor, N-acetylcysteine (N-Ac), ideally within 12 hours of overdose, prevents life-threatening liver injury, and assures recovery [46]. Later administration may limit the liver injury, but its utility decreases with time [46,8]. In the presence of a sufficiently large overdose, the administration of N-Ac beyond a certain time window becomes futile. In these cases, liver transplantation becomes the only life-saving measure.

A number of factors may determine whether a dose of APAP is fatal. Among the most important are the size of the overdose and the time to first administration of N-Ac [46]. Unfortunately, these two values are frequently not available at the time of admission to hospital: patients often arrive confused or comatose, the family is usually unaware of the

timing or the dose of drug taken, and concomitant use of other medications or drugs often obscures the clinical picture.

We therefore sought a method for rapidly determining the time of overdose, extent of injury, and likelihood of spontaneous survival using laboratory data available at the time of admission. Our method is based on a mathematical model that describes typical hepatic injury progression, dependent only on overdose amount. Fitting patient lab values to our mathematical model allows for the estimation of overdose amount and timing, as well as a prediction of outcome. We tested the mathematical model on 53 patients from the University of Utah.

## 2 Methods

### 2.1 Model Background

Our mathematical model, the Model of Acetaminophen-induced Liver Damage (MALD), is based on a reproducible pattern of APAP-induced liver injury. The enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are released by injured hepatocytes [9,10]. These enzymes peak at about 36 hours from initial injury, and have distinct injury and clearance curves. AST concentration in blood is initially approximately double that of ALT, with a clearance rate of about 50% every 24 hours. ALT peaks at the same time as AST, but with a slower elimination rate of about 33% every 24 hours [11]. These measures of damage are complemented by a measure of liver function, prothrombin time/international normalized ratio (INR). Decreased production of essential clotting factors manifests as reduced clotting and increased INR, again with

characteristic rates of increase and decay [12]. The values of AST, ALT, and INR at the time of admission thus encode the course of disease progression over time, and can be used, with a suitable mathematical model, to estimate initial dose and time of overdose.

## 2.2 Model description

We developed a system of nonlinear ordinary differential equations to describe the temporal dynamics of APAP-induced ALF based on known mechanisms of acetaminophen metabolism (Supplementary Information). The equations describe NAPQI production from acetaminophen metabolism, glutathione conjugation, hepatocyte death by NAPQI, release and clearance of AST and ALT in the blood, hepatocyte regeneration, and clotting factor production (figure 1). The variables and parameters can be divided into those describing hepatocyte, acetaminophen, glutathione, INR, and AST/ALT dynamics.

Functional hepatocytes ($H$) become damaged hepatocytes ($Z$) and regenerate with the following parameters:

- the number of hepatocytes in a healthy liver is $H_{max}$=1.6*10$^{11}$ [14]
- damaged hepatocytes lyse with rate $\delta_z$=5/day
- functional hepatocytes regenerate with rate $r$=1/day [15]
- functional hepatocytes become damaged with rate $\eta$= 5.12*10$^{13}$ cell/mol/day

- the fraction of liver required for survival is $\mu$= 0.3 [16].

Serum APAP (*A*) is a surrogate for liver APAP which is converted to NAPQI (*N*) with the following parameters:

- APAP is cleared by hepatocytes with rate $\alpha$= 6.3/day [17]
- APAP is cleared unconjugated with rate $\delta_a$= 0.33/day [2,3]
- the fraction of APAP that is oxidized to NAPQI is *p*=0.05 [2,3]
- the conversion factor from grams of APAP to mol of NAPQI is *q*=0.0067 mol/g.

GSH (G) is associated with the following parameters:

- GSH binds to NAPQI with rate $\gamma$= 1.6*10$^{18}$ cell/mol/day [18]
- GSH decays with rate $\delta_g$=2/day [19] [20] [21]
- GSH is produced with rate $\kappa$ = 1.375*10$^{-14}$ mol/cell/day.

INR (*I*) is related to the clotting factor concentration as a fraction of normal (*F*) and is associated with the following parameters:

- clotting factor VII is cleared with rate $\beta_f$=5/day [22]
- the minimum clotting factor concentration is $F_{min}$=0.75.

Serum AST concentration (*S*) and serum ALT concentration (*L*) increase and decay with the following parameters:

- AST is cleared with rate $\delta_s$=0.92/day [11]
- ALT is cleared with rate $\delta_l$=0.35/day [11]
- the total amount of AST in a healthy liver is $\beta_s$=200,000 IU
- the total amount of ALT in a healthy liver is $\beta_l$=84,800 IU
- the amount of blood in a human body is $\theta$ = 5 L
- the minimum AST level is $S_{min}$=12 IU/L
- the minimum ALT level is $L_{min}$=9 IU/L.

Six parameters were adjusted to match properties of the data, independent of patient survival information. The amounts of AST and ALT in the liver, $\beta_s$ and $\beta_l$, respectively, were scaled to the maximum observed AST and ALT values, and the minimum AST and ALT levels, $S_{min}$ and $L_{min}$, respectively, were scaled to the minimum observed AST and ALT values. The minimum clotting factor concentration $F_{min}$ was scaled to the maximum observed INR value. The damaged hepatocyte lysis rate $\delta_z$ was adjusted to the timing of peak AST and ALT values.

Two parameters were scaled to the dose of APAP required for hepatotoxicity and death. The glutathione production rate, $\kappa$, was scaled to the dosage at which glutathione reserves are depleted. The minimum dosage predicted to lead to hepatotoxicity varies, but typically ranges from 7.5 to 10 gm for an adult [8,23]. We chose a slightly lower value of 6.0 gm for the dosage at which glutathione reserves are depleted. The rate at which

hepatocytes become damaged by NAPQI, $\eta$, is a scaling factor that was chosen so that a 20 gram overdose is equivalent to 70% hepatic necrosis and predicted death.

### 2.3 Patients

Between January 1, 2006 and December 31, 2009 all hospital discharges from the University of Utah were queried for the diagnosis of severe, acute APAP toxicity. Charts were excluded if they included acute hepatitis A or B, autoimmune hepatitis, Wilson disease, or multisystem failure. Laboratory data, and admission and discharge notes were further reviewed to identify cases in which acute liver disease was due to APAP overdose only. Charts that had overdose with additional medications were not included in this analysis. Demographics, N-Ac administration, and medical outcome information were collected. Laboratory results of AST, ALT, INR, bilirubin, and creatinine were also collected. Charts without at least one measure of AST, ALT, and INR were excluded from the study. In total, 53 patients were included. The patient population was diverse, with varying alcohol use, body mass index, and ingestion type, including suicide attempts, single accidental overdoses, and multiple day chronic overdoses.

#### 2.3.1 Ethics statement

Patient consent was not obtained since data were retrospective, were based on standard care, and were analyzed anonymously. The protocol was approved by the IRB of the University of Utah in accordance with the Declaration of Helsinki.

### 2.4 Serum creatinine

Serum creatinine was added as an additional criterion separate from the model since it is a marker of kidney damage, and our dynamic model does not describe kidney damage. Since kidney function is ultimately important in survival in APAP overdose, patients with serum creatinine greater than 3.4 mg/dL were predicted to die [24].

### 2.5 Fitting the model to individual patients

Upon admission, before administration of N-Ac, a patient's AST, ALT, and INR values in the mathematical model are a function of two parameters, APAP overdose amount, $A_0$, and time since overdose, $\tau$. These two parameters were estimated using weighted least squares and values of AST, ALT, and INR on admission. The weights were determined by post-treatment model fits (see Supplementary Information for more detail). To test the sensitivity of predicted outcomes to changes in parameters, we increased and decreased each parameter by 50% of its original value and fit individuals to the model, keeping track of the predicted outcome for each patient.

## 3 Results

We tested the model on 53 patients from the University of Utah. The time since overdose and overdose amount were estimated for each patient using initial measurements of AST, ALT, and INR on admission (figure 2). Based on the extent of estimated liver injury, the model predicts death for patients who took over 20 grams of APAP without N-Ac administration within the first 24 hours.

Excluding patients who were transplanted, death versus recovery can be predicted with 75% sensitivity and 95% specificity (table 1). With the addition of initial serum creatinine exceeding 3.4 mg/dL, sensitivity increased to 100%. For this data set, the subset of the King's College Criteria (KCC) to which we had access (INR > 6.5 and creatinine > 3.4 mg/dL) had 13% sensitivity and 100% specificity. Only one patient had both INR > 6.5 and creatinine > 3.4 on admission. Thinking of the KCC as either INR > 6.5 or creatinine > 3.4 mg/dL increases sensitivity to 88%. We did not have access to patient encephalopathy or arterial pH.

Using only data available on admission, the model results fit the post-treatment time-series of the markers of liver damage for the majority of individual patients (Supplementary Information table 2). The results from four representative patients are shown in figure 3. Patients 5 and 8 were predicted to have had overdoses that were very close to the lethal threshold, whereas patient 49 was predicted to have exceeded the lethal threshold. Patient 16 was predicted to have had a smaller overdose. The confidence region for some patients who recovered (e.g. patient 16) includes regions with high overdose amount and very early N-Ac administration, as well as regions with low overdose amount and late N-Ac administration. In both cases AST, ALT, and INR are low.

Model predictions of outcome were robust to 50% increase or decrease in parameter values (Supplementary Information table 3). The most sensitive model parameters were the fraction of liver required for survival, $\mu$, and the amount of AST in the liver, $\beta_s$.

Increasing $\mu$ to 0.45 caused more patients who eventually recovered to be predicted to die, and resulted in 100% sensitivity and 77% specificity, while decreasing $\mu$ to 0.15 resulted in 88% sensitivity and 93% specificity. Increasing $\beta_s$ by 50% resulted in 100% sensitivity and 79% specificity, while decreasing $\beta_s$ by 50% resulted in 88% sensitivity and 88% specificity.

Some parameters such as *p*, the fraction of APAP oxidized to NAPQI, have a large effect on predicted dose of APAP, but no effect on predicted outcome. If *p* is 0.025, an overdose amount of 40 grams is required for 70% hepatic necrosis and predicted death, while if *p* is 0.075, an overdose amount of 13.3 grams is required for 70% hepatic necrosis and predicted death. Estimates of overdose amount scale with lethal dose so that estimates of outcome remain the same despite large changes in estimated overdose amount.

## 4 Discussion

APAP, alone or in combination, accounts for about 50% of cases of ALF in the USA [25]. Survival largely depends on two parameters: the size of the initial dose and time elapsed prior to the administration of N-Ac. Very early administration (up to 12 hours after overdose) of N-Ac results in almost 100% survival [46].

Some models of APAP toxicity rely on the time between ingestion and hospital admission to determine the need for treatment [17] or as a measure of exposure [26].

These are risky approaches because the timing of the overdose provided by the patient is frequently unobtainable or unreliable. Moreover, patients who arrive at the hospital 24 hours or more post-ingestion may have plasma acetaminophen levels below the detection limit.

The King's College Criteria (KCC) [24] provide a well-validated method for predicting death without transplantation in APAP-induced ALF [37], although they have been criticized for low sensitivity [38] and low negative predictive value [39]. KCC used an initial data set of 310 patients to identify statistically significant prognostic indicators to distinguish survivors and nonsurvivors and used a validation set of 121 patients to identify cutoff values associated with survival rates less than 20% for the statistically significant prognostic indicators, with no physiologically defined model of mortality. Many modifications of the KCC have been suggested [e.g. 40-45], perhaps most importantly the addition of arterial lactate [47]. Arterial lactate has consistently been shown to be associated with survival, although its prognostic value has been questioned [48].

In contrast to other modifications of the KCC, MALD is novel because we build upon the KCC by utilizing an understanding of the dynamics of hepatocyte damage following APAP overdose in the form of a dynamic mathematical model. Hepatic necrosis is directly related to the extent of covalent binding of NAPQI to intracellular components [6,7,4,2], which causes hepatocyte lysis and release of AST and ALT into the blood. This produces a characteristic time course of injury with an early rise and predictable decay of

AST, ALT, and INR. We have developed a system of differential equations based on the principles of APAP-induced liver damage. All parameters in MALD were estimated from the literature, except six that were adjusted to match general properties of AST and ALT dynamics, and two that were scaled to the dosages thought to cause hepatotoxicity and death. Survival information from University of Utah patients was not used in model development or parameterization. The equations describe how AST, ALT, and INR levels change over time as a function of overdose amount. Since these curves over time are only a function of initial overdose amount, AST, ALT, and INR levels in the model only depend on initial overdose amount and time since overdose. Our method works by fitting measured AST, ALT, and INR values to the curves described by our differential equations to estimate overdose timing and amount (figure 4). An outcome of death is predicted when the estimate of overdose amount is sufficiently high and the estimate of timing predicts N-Ac to be ineffectual, or when serum creatinine measurements are sufficiently high. If the outcome is predicted to be poor, liver transplantation may be the only life-saving treatment.

Previous studies have not found absolute aminotransferase levels to be significant predictors of outcome in cases of APAP-induced ALF (e.g. [24]). This is not surprising because aminotransferase levels will be low, even with a high dose, both early and late in the course of the injury based on known mechanisms of liver damage following APAP overdose. Similarly, high aminotransferase levels may be measured near peak liver damage, even in cases of non-lethal overdose. In conjunction with INR and a suitable

mathematical model describing these mechanisms, however, aminotransferase levels do contain sufficient information to estimate the timing and amount of overdose.

Our model cannot distinguish patients with high overdose amounts and early administration of N-Ac from patients with low overdose amounts and delayed treatment because in both cases AST, ALT, and INR levels are low. However, this ambiguity affects only patients who are predicted to recover.

Some patients with unique characteristics, such as those with significant muscle damage, may not fit the model. Muscle damage increases the level of AST, which may lead to poor estimation of liver damage. Since ALT and INR values are not affected by muscle damage, this effect may be minimal. Further studies are warranted to determine whether more refinements are needed for special patient groups.

Our treatment of all patients as having the same parameter values is unrealistic. Well-known covariates of disease severity such as age [27], chronic alcohol use [28,29], starvation or malnutrition [30], and interactions with other drugs [31,32,33] may affect the parameter values of an individual. In some cases these differences will not affect the accuracy of predictions of outcome. Model predictions derive from the amount of unconjugated NAPQI that results from a given dose, but that amount may depend on patient characteristics. For example, alcoholics may make excessive NAPQI because of elevated p-450 levels, or individuals may have decreased levels of GSH because of starvation, competition from other drugs, or genetic variation. These differences might

make the model estimates of initial dose seem overly high, but the outcome could still be accurately predicted because these patients have more unconjugated NAPQI than is typical for the overdose amount.

James et al. [34] show that acetaminophen protein adduct levels may be used as specific biomarkers of APAP toxicity. If measurements were routinely available, adducts could easily be added to our model, and might provide additional predictive value. However, the correlation of protein adducts with AST and their similar kinetics lead us to predict this effect would be small, although their more direct relationship to liver damage might reduce noise and make them a superior predictor.

Gregory et al. [35] found that individuals with overdose amounts greater than 10 grams did not have significantly different mortality than those reporting smaller overdoses in patients with eventual hepatic encephalopathy. The authors suggest that this may be due to inaccurate reporting of dosing information by patients with eventual hepatic encephalopathy, or from a plateau effect in APAP overdose amount, such that above a threshold, the effect of APAP overdose ceases to be additive. A plateau is built into our model, but at 20 grams rather than 10 grams. In our model, without treatment, any overdose above 20 grams will result in severe hepatic injury resulting in maximal AST, ALT, and INR levels and poor outcome. Our patient set is quite different since Gregory et al. required eventual hepatic encephalopathy for inclusion, a parameter unknown on admission and associated with poor prognosis [36].

Methods to determine whether to use dangerous and costly interventions, such as transplantation, will ideally be based on clinical data that are readily available at the time of admission. Using only initial measurements of AST, ALT and INR, we were able to predict the hepatic injury progression and extent of liver damage following APAP overdose. Unlike statistical models to predict outcome, which must build upon survivorship data, our mechanistic approach is based on the independently testable assumption that 70% hepatic necrosis leads to death. Our dynamic model yields a prediction of outcome by estimating the time since overdose and overdose amount from commonly obtained laboratory data on admission. With the inclusion of creatinine, we were able, in this retrospective analysis, to predict survival vs. death with 91% specificity, 100% sensitivity, 67% PPV, and 100% NPV. Our initial analysis suggests that MALD compares favorably to statistical methods, and should be validated in multicentric retrospective and prospective evaluation.

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## 6 Supplementary Information

### 6.1 Model equations

The dynamics of total serum APAP ($A$), intracellular NAPQI concentration ($N$), intracellular GSH concentration ($G$), number of functional hepatocytes ($H$), number of damaged hepatocytes ($Z$), serum AST concentration ($S$), serum ALT concentration ($L$),

and serum clotting factor concentration ($F$) are governed by the following system of ordinary differential equations:

APAP $$\frac{dA}{dt} = -\frac{\alpha}{H_{max}} AH - \delta_a A$$

NAPQI $$\frac{dN}{dt} = \frac{qp\alpha}{H_{max}} A - \gamma NG$$

GSH $$\frac{dG}{dt} = \kappa - \gamma NG - \delta_g G$$

Functional Hepatocytes $$\frac{dH}{dt} = rH\left(1 - \frac{H+Z}{H_{max}}\right) - \eta NH$$

Damaged Hepatocytes $$\frac{dZ}{dt} = \eta NH - \delta_z Z$$

AST $$\frac{dS}{dt} = \frac{d_z \beta_s}{\theta H_{max}} Z - \delta_s (S - S_{min})$$

ALT $$\frac{dL}{dt} = \frac{d_z \beta_l}{\theta H_{max}} Z - \delta_l (L - L_{min})$$

Clotting Factor $$\frac{dF}{dt} = \beta_f \left(\frac{H}{H_{max}} - F\right)$$

APAP is cleared by conjugation at rate $\alpha \frac{H}{H_{max}}$, and a small amount is cleared unconjugated at rate $\delta_a$. A fraction $p$ of the APAP is converted to NAPQI and is cleared at rate $\gamma G$. GSH has a constant production $\kappa$ and decays at rate $\delta_g$. Hepatocytes grow

logistically with rate *r* saturating at $H_{max}$ and become damaged at rate $\eta N$ releasing AST and ALT into the blood at rates $\frac{d_z\beta_s}{\theta H_{max}}$ and $\frac{d_z\beta_l}{\theta H_{max}}$, respectively. Clotting factors are produced by hepatocytes and decay at a rate $\beta_f$. INR (*I*) is related to the concentration of clotting factors by the algebraic equation $I = \left(\frac{1+F_{min}}{F+F_{min}}\right)^4$.

### 6.2 Post-treatment model fits

To estimate uncertainty in measurements of AST, ALT, and INR, we define a post-treatment model as a special case of the pre-treatment model. Treatment with N-Ac leads to a high concentration of intracellular GSH, preventing further damage to hepatocytes (i.e. $N$=0). This reduces the AST subsystem to

$$\frac{dZ}{dt} = -\delta_z Z$$

$$\frac{dS}{dt} = \frac{d_z\beta_s}{\theta H_{max}} Z - \delta_s\left(S - S_{min}\right),$$

the ALT subsystem to

$$\frac{dZ}{dt} = -\delta_z Z$$

$$\frac{dL}{dt} = \frac{d_z \beta_l}{\theta H_{max}} Z - \delta_l (L - L_{min}),$$

and the INR subsystem to

$$\frac{dZ}{dt} = -\delta_z Z$$

$$\frac{dH}{dt} = rH\left(1 - \frac{H+Z}{H_{max}}\right)$$

$$\frac{dF}{dt} = \beta_f \left(\frac{H}{H_{max}} - F\right)$$

$$I = \left(\frac{1+F_{min}}{F+F_{min}}\right)^4.$$

The post-treatment model subsystems were fit to individual patients using least squares. In the AST subsystem, the modeled AST value is a function of two parameters, the modeled AST concentration at the time of admission, $S_0$, and the number of damaged hepatocytes on admission, $Z_0$. For each individual patient, the best fit solution is the one that minimizes, over all possible combinations of $S_0$ and $Z_0$, the sum of the squared residual

$$\sum_i \left(\log(AST_i) - \log(S_i(S_0, Z_0))\right)^2,$$

where $AST_i$ is the patient's measured AST value $i$ days after the first measurement, and $S_i(S_0,Z_0)$ is the modeled AST value $i$ days after the first measurement with initial conditions $S_0$ and $Z_0$. All logarithms indicate the natural log. The residual for each measurement is defined as $\log(AST_i)-\log(S_i(S^*_0,Z^*_0))$ where $S^*_0$ and $Z^*_0$ are the AST and damaged hepatocyte initial conditions that minimize the least squares problem, respectively. The standard deviation of all of the residuals from all measurements of AST from all patients is $\omega_s$=0.60.

Using the same approach described above, but replacing $AST_i$, $S_i$, and $S_0$ by $ALT_i$, $L_i$, and $L_0$, respectively, the standard deviation of all of the residuals from all measurements of ALT from all patients is $\omega_l$=0.43.

For INR, the modeled value $I_i$ depends on three parameters, modeled clotting factor concentration at the time of admission, $F_0$, modeled number of damaged hepatocytes at admission, $Z_0$, and modeled number of functional hepatocytes at admission, $H_0$. Again minimizing the least squares difference between measured $INR_i$ and modeled $I_i(F_0, Z_0, H_0)$, the standard deviation of the residuals from all measurements of all patients is $\omega_i$=0.26.

**6.3 Pre-treatment model fits**

For each patient, the estimated overdose amount $A_0$ and $\tau$ are those that minimize

$$R = \left( \frac{\log(AST) - \log(S(A_0, \tau))}{\omega_s} \right)^2 + \left( \frac{\log(ALT) - \log(L(A_0, \tau))}{\omega_l} \right)^2 + \left( \frac{\log(INR) - \log(I(A_0, \tau))}{\omega_i} \right)^2$$

where *AST*, *ALT*, and *INR* are a patient's measured AST, ALT, and INR on admission, and *S*, *L*, and *I* are modeled AST, ALT, and INR for overdose amount $A_0$ at time $\tau$ since overdose.

The confidence regions of $A_0$ and $\tau$ for individual patients in figure 3 are defined as follows. We begin with the best least squares estimate for $A_0$ and $\tau$, where the residual *R* takes its minimum $R^*$. We then find regions $A_0$ and $\tau$ for which *R* is within 0.5 of $R^*$, *R* exceeds $R^*$ by 0.5 to 1, *R* exceeds $R^*$ by 1 to 1.5, and *R* exceeds $R^*$ by 1.5 to 2.

The line separating predicted recovery and predicted death in figure 2 was determined by numerically solving the full pre-treatment model for a range of $A_0$, marking the time since overdose when *H* equals 30% of its initial value (i.e. 70% hepatic necrosis occurs). The estimated probability of death for each patient is calculated as the fraction of *R* within 2 of $R^*$ for which $A_0$ and $\tau$ lie in the region of predicted death.

To test the sensitivity of model predictions to parameters, we fit patients to the pre-treatment model with each parameter perturbed by 50% and 150% of its original value. A summary of how each parameter perturbation affects sensitivity, specificity, PPV, and NPV is shown in table 3. Predicted outcomes were robust to changes in parameter values.

## 7 Table and Figure Legends

Table 1: Sensitivity, specificity, PPV, and NPV for a subset of King's College Criteria (INR > 6.5 and creatinine > 3.4 mg/dL), either INR > 6.5 or creatinine > 3.4 mg/dL, and the current study both with and without creatinine as an independent marker. Absolute numbers and 95% Clopper-Pearson confidence interval are given in parentheses.

Table 2 (Supplementary Information): Observed AST, ALT, INR, creatinine, and result, and predicted overdose amount $A_0$, time since overdose $\tau$, predicted result without creatinine, residual, and estimated probability of death. Patients with predicted results marked with a star (*) were predicted to die with the inclusion of creatinine.

Table 3 (Supplementary Information): A summary of how changes in parameter values affect predictions of outcome.

Figure 1: A schematic diagram representing the dynamics of the mathematical model. A fraction of APAP is oxidized to NAPQI, bound to GSH, and safely eliminated. As GSH stores are depleted, NAPQI damages hepatocytes, releasing AST and ALT into the blood.

Meanwhile, functional hepatocytes regenerate and produce essential clotting factors. Red represents the intracellular variables, yellow represents healthy and damaged hepatocytes, and blue represents markers of liver damage.

Figure 2: MALD derived estimates of time since overdose and overdose amount for 53 patients with known APAP overdose. Red squares indicate eventual death, green circles recovery, and orange triangles transplant. Small white dots indicate INR > 6.5 and small black dots indicate serum creatinine > 3.4 mg/dL on admission. The grey line indicates overdose amounts and times since overdose for which 70% hepatic necrosis is predicted. Patients to the right and above the grey line are predicted to die.

Figure 3: Markers of liver damage (small black open circles) and model predictions (red dashed line) based on least squares fits of initial AST, ALT, and INR (large black filled circle) to modeled AST, ALT, and INR (large red filled circle) for four representative patients. Time t=0 indicates the time of admission to hospital. The estimated overdose amount and time since overdose for each patient is given by the orange dot in the lower right panel. Refer to the Supplementary Information for more detail.

Figure 4: A schematic description of how MALD can be used to estimate overdose amount, timing and outcome. Patient AST, ALT, and INR are fit to a family of curves described by MALD to estimate overdose amount, timing, and outcome. If outcome is predicted to be poor, liver transplantation may be necessary.

| Model | Specificity | Sensitivity | PPV | NPV |
|---|---|---|---|---|
| | | | | |
| INR > 6.5 and creatinine > 3.4 mg/dL | 1 (43/43, 0.92-1) | 0.13 (1/8, 0-0.53) | 1 (1/1, 0-1) | 0.86 (43/50, 0.73-0.94) |
| INR > 6.5 or creatinine > 3.4 mg/dL | 0.95 (41/43, 0.84-0.99) | 0.88 (7/8, 0.47-1) | 0.78 (7/9, 0.4-0.97) | 0.98 (41/42, 0.87-1) |
| MALD (No Creatinine) | 0.95 (41/43, 0.84-0.99) | 0.75 (6/8, 0.35-0.97) | 0.75 (6/8, 0.35-0.97) | 0.95 (41/43, 0.84-0.99) |
| MALD (With Creatinine) | 0.91 (39/43, 0.78-0.97) | 1 (8/8, 0.63-1) | 0.67 (8/12, 0.35-0.90) | 1 (39/39, 0.91-1) |
| | | | | |

Table 1

| patient number | AST | ALT | INR | creatinine | result | $A_0$ | $\tau$ | predicted result (without creatinine) | residual | probability of death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18 | 27 | 1.2 | 0.8 | recovery | 6.1 | 3.9 | recovery | 0.5 | 0 |
| 3 | 138 | 128 | 1.2 | 0.5 | recovery | 6.6 | 1.9 | recovery | 0.46 | 0 |
| 4 | 6023 | 3352 | 11 | 1.5 | transplant | 25.1 | 4.4 | death | 3.73 | 1 |
| 5 | 6432 | 6390 | 3 | 3 | recovery | 18.9 | 3.2 | recovery | 0.23 | 0.12 |
| 6 | 5267 | 12202 | 4.3 | 0.6 | recovery | 20.5 | 3.4 | death | 0.82 | 0.44 |
| 8 | 11842 | 6731 | 3.9 | 2.6 | recovery | 16.3 | 1.6 | recovery | 0.46 | 0.15 |
| 9 | 2381 | 4960 | 1.6 | 0.8 | recovery | 18.5 | 4.2 | recovery | 0.03 | 0.16 |
| 10 | 26 | 19 | 1.1 | 0.7 | recovery | 5.8 | 1.4 | recovery | 0.13 | 0 |
| 11 | 1546 | 3642 | 1.4 | 0.7 | recovery | 17.9 | 4.6 | recovery | 0.26 | 0.18 |
| 14 | 313 | 402 | 1.1 | 0.6 | recovery | 7.6 | 2.5 | recovery | 0.09 | 0 |
| 16 | 1427 | 1497 | 1.2 | 0.8 | recovery | 9.6 | 2.2 | recovery | 0.1 | 0 |
| 17 | 29 | 18 | 1.1 | 0.6 | recovery | 5.8 | 0.8 | recovery | 0.13 | 0 |
| 18 | 17 | 11 | 1.3 | 0.4 | recovery | 7.1 | 0.2 | recovery | 1.04 | 0 |
| 21 | 14230 | 6746 | 10.5 | 2.7 | death | 22.2 | 2.9 | death | 1.36 | 0.99 |
| 22 | 52 | 21 | 1 | 0.6 | recovery | 8.1 | 0.2 | recovery | 0.11 | 0 |
| 25 | 184 | 48 | 1 | 0.7 | recovery | 17.3 | 0.1 | recovery | 0.58 | 0 |
| 26 | 15953 | 5598 | 2 | 2.8 | recovery | 40 | 0.4 | recovery | 0.46 | 0 |
| 28 | 28 | 17 | 1.1 | 0.8 | recovery | 5.8 | 0.7 | recovery | 0.13 | 0 |
| 29 | 10394 | 8392 | 3.7 | 5 | death | 17.5 | 2.4 | recovery* | 0.02 | 0.14 |
| 31 | 24 | 16 | 1.1 | 0.6 | recovery | 5.7 | 1 | recovery | 0.14 | 0 |
| 33 | 774 | 443 | 1.7 | 0.7 | recovery | 7.3 | 0.8 | recovery | 3.44 | 0 |
| 36 | 509 | 7686 | 3.3 | 4 | death | 25.1 | 6 | death* | 2.84 | 1 |
| 37 | 53 | 19 | 1.1 | 0.5 | recovery | 9.9 | 0.1 | recovery | 0.39 | 0 |
| 38 | 69 | 71 | 1 | 1 | recovery | 6.3 | 2.2 | recovery | 0 | 0 |
| 39 | 8122 | 8134 | 3.8 | 0.8 | recovery | 19 | 2.9 | recovery | 0.03 | 0.17 |
| 41 | 443 | 3368 | 1.9 | 0.8 | recovery | 24.7 | 6.6 | death | 0.01 | 1 |
| 43 | 23 | 22 | 1.2 | 0.7 | recovery | 5.9 | 2.3 | recovery | 0.5 | 0 |
| 44 | 35 | 19 | 1.2 | 0.7 | recovery | 6 | 0.4 | recovery | 0.5 | 0 |
| 47 | 23 | 21 | 1.2 | 0.6 | recovery | 5.9 | 2.1 | recovery | 0.5 | 0 |
| 49 | 7454 | 5507 | 17.8 | 1.4 | death | 25.7 | 3.9 | death | 1.19 | 1 |
| 51 | 37 | 27 | 1.4 | 0.9 | recovery | 5.9 | 1.4 | recovery | 1.69 | 0 |
| 53 | 626 | 563 | 1.6 | 0.7 | recovery | 7.7 | 1.7 | recovery | 2.75 | 0 |
| 54 | 24000 | 15000 | 3.1 | 0.9 | recovery | 17 | 1.2 | recovery | 2.84 | 0.14 |
| 55 | 289 | 1884 | 1.1 | 0.6 | recovery | 15.1 | 5.9 | recovery | 0.07 | 0.31 |
| 58 | 21 | 35 | 1.2 | 0.7 | recovery | 6.2 | 3.9 | recovery | 0.5 | 0 |
| 59 | 5238 | 3641 | 17.3 | 2.8 | death | 26.4 | 4.5 | death | 2.65 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 6298 | 2792 | 21.1 | 3.8 | death | 27.1 | 4.5 | death* | 5.3 | 1 |
| 61 | 230 | 921 | 1.7 | 6.7 | transplant | 10.5 | 4.7 | recovery* | 4.03 | 0.29 |
| 62 | 744 | 903 | 1.5 | 0.9 | recovery | 8.6 | 2.3 | recovery | 1.89 | 0 |
| 63 | 8029 | 6989 | 2 | 1 | recovery | 14.6 | 2.2 | recovery | 0.1 | 0 |
| 65 | 147 | 117 | 1.3 | 0.6 | recovery | 6.5 | 1.6 | recovery | 0.97 | 0 |
| 67 | 21 | 9 | 1.2 | 1 | recovery | 13.9 | 0.1 | recovery | 0.86 | 0 |
| 68 | 1621 | 1404 | 1.8 | 5.5 | recovery | 8.9 | 1.3 | recovery* | 3.11 | 0 |
| 71 | 10810 | 9218 | 4.4 | 2.4 | recovery | 18.4 | 2.5 | recovery | 0 | 0.23 |
| 74 | 5562 | 4449 | 2.2 | 3.5 | death | 13.1 | 1.7 | recovery* | 0.76 | 0.05 |
| 75 | 14520 | 9159 | 2.3 | 1.3 | recovery | 14.4 | 1.6 | recovery | 0.85 | 0.02 |
| 77 | 1545 | 1228 | 6.3 | 1.2 | death | 26.7 | 6.3 | death | 8.26 | 1 |
| 78 | 7716 | 5588 | 2.3 | 0.7 | recovery | 13.9 | 1.8 | recovery | 0.15 | 0 |
| 79 | 37 | 13 | 1.2 | 0.8 | recovery | 15.9 | 0.1 | recovery | 0.92 | 0 |
| 81 | 31 | 25 | 1.1 | 0.7 | recovery | 5.9 | 1.7 | recovery | 0.13 | 0 |
| 82 | 115 | 163 | 1.5 | 3.1 | recovery | 6.9 | 2.7 | recovery | 2.41 | 0 |
| 83 | 78 | 52 | 1.5 | 0.7 | recovery | 6.1 | 1.2 | recovery | 2.43 | 0 |
| 84 | 17161 | 12147 | 4.2 | 3.5 | recovery | 17.5 | 1.5 | recovery* | 0.42 | 0.23 |

Table 2 (Supplementary Information)

| Modified Parameter | New Value | Specificity | Sensitivity | PPV | NPV |
|---|---|---|---|---|---|
| Current Study (With Creatinine) | | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\mu$ | 0.45 | 0.77 (33/43) | 1 (8/8) | 0.44 (8/18) | 1 (33/33) |
| $\mu$ | 0.15 | 0.93 (40/43) | 0.88 (7/8) | 0.7 (7/10) | 0.98 (40/41) |
| $H_{max}$ | $2.4*10^{11}$ | 0.93 (40/43) | 1 (8/8) | 0.73 (8/11) | 1 (40/40) |
| $H_{max}$ | $8*10^{10}$ | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\beta_f$ | 7.5 | 0.88 (38/43) | 0.88 (7/8) | 0.58 (7/12) | 0.97 (38/39) |
| $\beta_f$ | 2.5 | 0.88 (38/43) | 1 (8/8) | 0.62 (8/13) | 1 (38/38) |
| $\eta$ | 480 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\eta$ | 160 | 0.93 (40/43) | 1 (8/8) | 0.73 (8/11) | 1 (40/40) |
| $\beta_l$ | 127200 | 0.88 (38/43) | 0.88 (7/8) | 0.58 (7/12) | 0.97 (38/39) |
| $\beta_l$ | 42400 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\beta_s$ | $3*10^5$ | 0.79 (34/43) | 1 (8/8) | 0.47 (8/17) | 1 (34/34) |
| $\beta_s$ | $1*10^5$ | 0.88 (38/43) | 0.88 (7/8) | 0.58 (7/12) | 0.97 (38/39) |
| $q$ | 0.01005 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $q$ | 0.00335 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_l$ | 0.525 | 0.88 (38/43) | 1 (8/8) | 0.62 (8/13) | 1 (38/38) |
| $\delta_l$ | 0.175 | 0.93 (40/43) | 0.88 (7/8) | 0.7 (7/10) | 0.98 (40/41) |
| $\delta_s$ | 1.38 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_s$ | 0.46 | 0.74 (32/43) | 0.88 (7/8) | 0.39 (7/18) | 0.97 (32/33) |
| $r$ | 1.5 | 0.84 (36/43) | 1 (8/8) | 0.53 (8/15) | 1 (36/36) |
| $r$ | 0.5 | 0.93 (40/43) | 1 (8/8) | 0.73 (8/11) | 1 (40/40) |
| $\kappa$ | 0.0033 | 0.91 (39/43) | 0.88 (7/8) | 0.64 (7/11) | 0.98 (39/40) |

| | | | | | |
|---|---|---|---|---|---|
| $\kappa$ | 0.0011 | 0.93 (40/43) | 0.88 (7/8) | 0.7 (7/10) | 0.98 (40/41) |
| $\delta_g$ | 3 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_g$ | 1 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_z$ | 7.5 | 0.93 (40/43) | 1 (8/8) | 0.73 (8/11) | 1 (40/40) |
| $\delta_z$ | 2.5 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\gamma$ | $1.5*10^7$ | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\gamma$ | $5*10^6$ | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $p$ | 0.075 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $p$ | 0.025 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_a$ | 0.495 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\delta_a$ | 0.165 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\alpha$ | 9.45 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $\alpha$ | 3.15 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $F_{min}$ | 0.85 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |
| $F_{min}$ | 0.65 | 0.93 (40/43) | 1 (8/8) | 0.73 (8/11) | 1 (40/40) |
| θ | 2.5 | 0.86 (37/43) | 0.88 (7/8) | 0.54 (7/13) | 0.97 (37/38) |
| θ | 7.5 | 0.91 (39/43) | 1 (8/8) | 0.67 (8/12) | 1 (39/39) |

Table 3 (Supplemental Information)

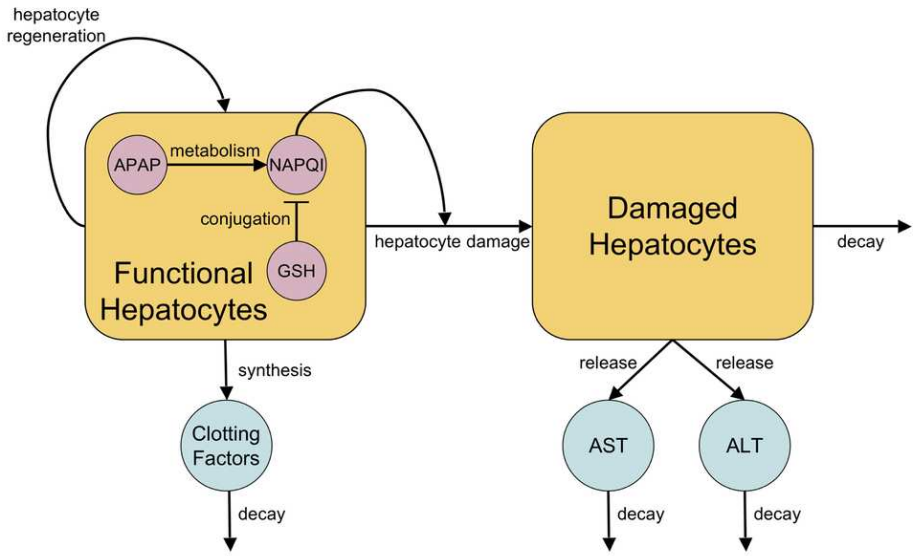


Figure 1: A schematic diagram representing the dynamics of the mathematical model. A fraction of APAP is oxidized to NAPQI, bound to GSH, and safely eliminated. As GSH stores are depleted, NAPQI damages hepatocytes, releasing AST and ALT into the blood. Meanwhile, functional hepatocytes regenerate and produce essential clotting factors. Red represents the intracellular variables, yellow represents healthy and damaged hepatocytes, and blue represents markers of liver damage.
44x34mm (600 x 600 DPI)

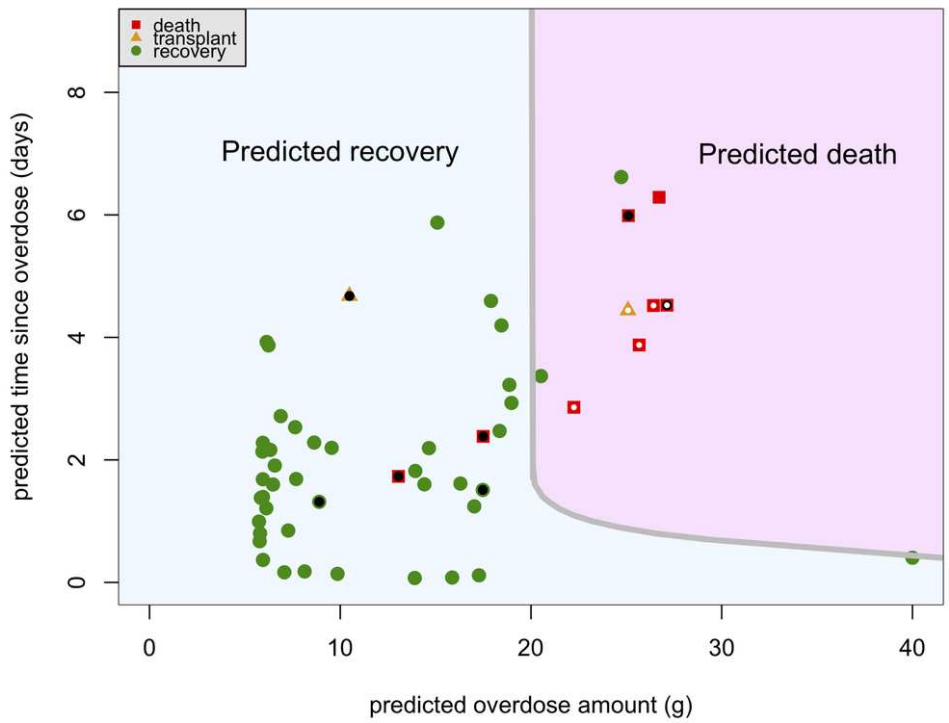


Figure 2: MALD derived estimates of time since overdose and overdose amount for 53 patients with known APAP overdose. Red squares indicate eventual death, green circles recovery, and orange triangles transplant. Small white dots indicate INR > 6.5 and small black dots indicate serum creatinine > 3.4 mg/dL on admission. The grey line indicates overdose amounts and times since overdose for which 70% hepatic necrosis is predicted. Patients to the right and above the grey line are predicted to die.
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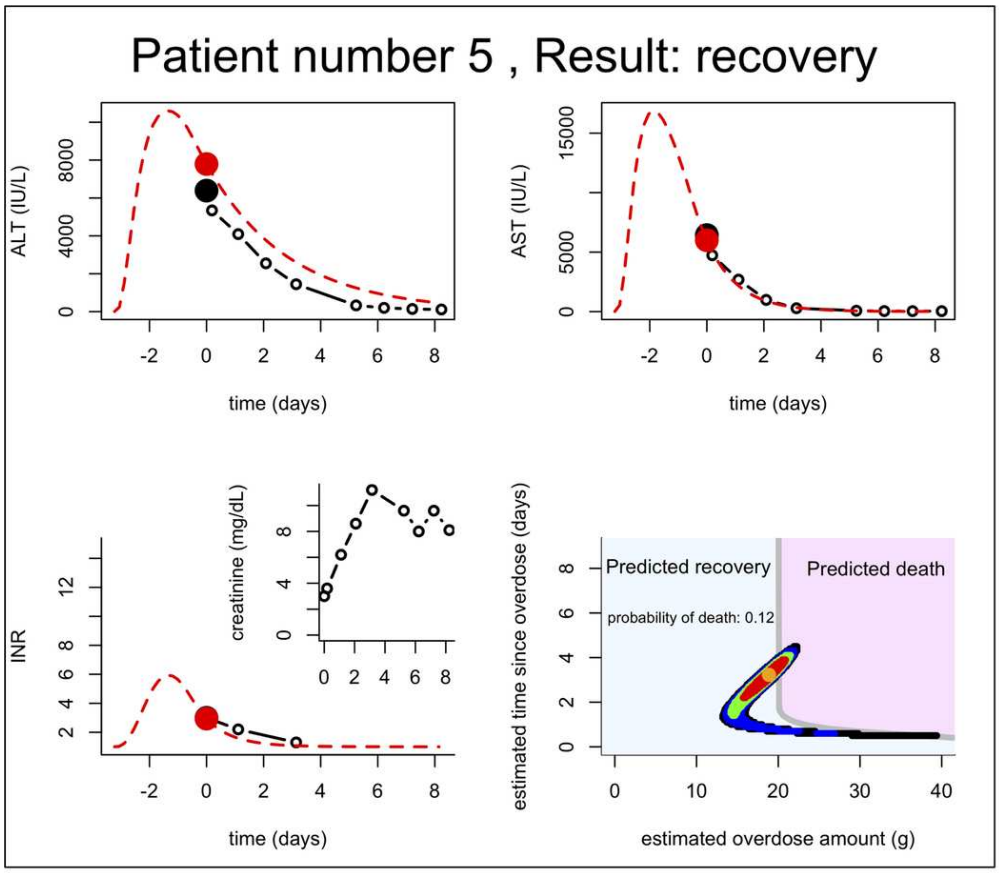



Figure 3A: Markers of liver damage (small black open circles) and model predictions (red dashed line) based on least squares fits of initial AST, ALT, and INR (large black filled circle) to modeled AST, ALT, and INR (large red filled circle) for four representative patients. Time t=0 indicates the time of admission to hospital. The estimated overdose amount and time since overdose for each patient is given by the orange dot in the lower right panel. Refer to the Supplementary Information for more detail.
44x38mm (600 x 600 DPI)

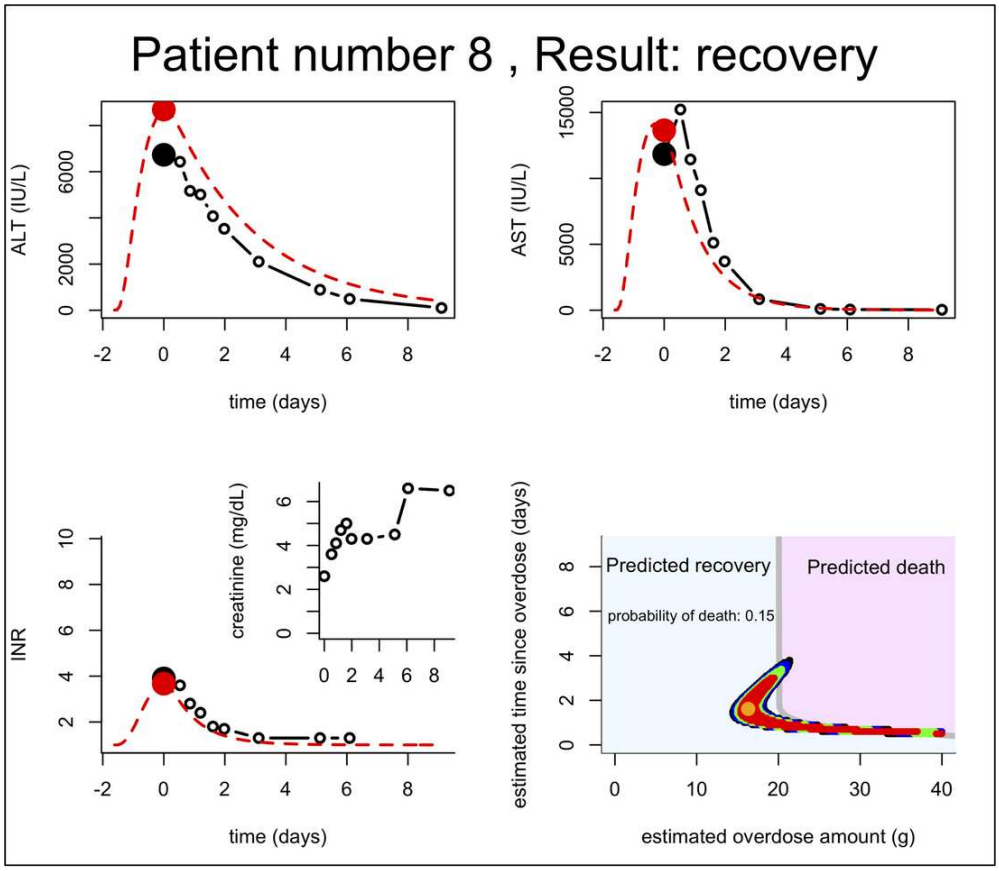



Figure 3B: Markers of liver damage (small black open circles) and model predictions (red dashed line) based on least squares fits of initial AST, ALT, and INR (large black filled circle) to modeled AST, ALT, and INR (large red filled circle) for four representative patients. Time t=0 indicates the time of admission to hospital. The estimated overdose amount and time since overdose for each patient is given by the orange dot in the lower right panel. Refer to the Supplementary Information for more detail.
46x40mm (600 x 600 DPI)

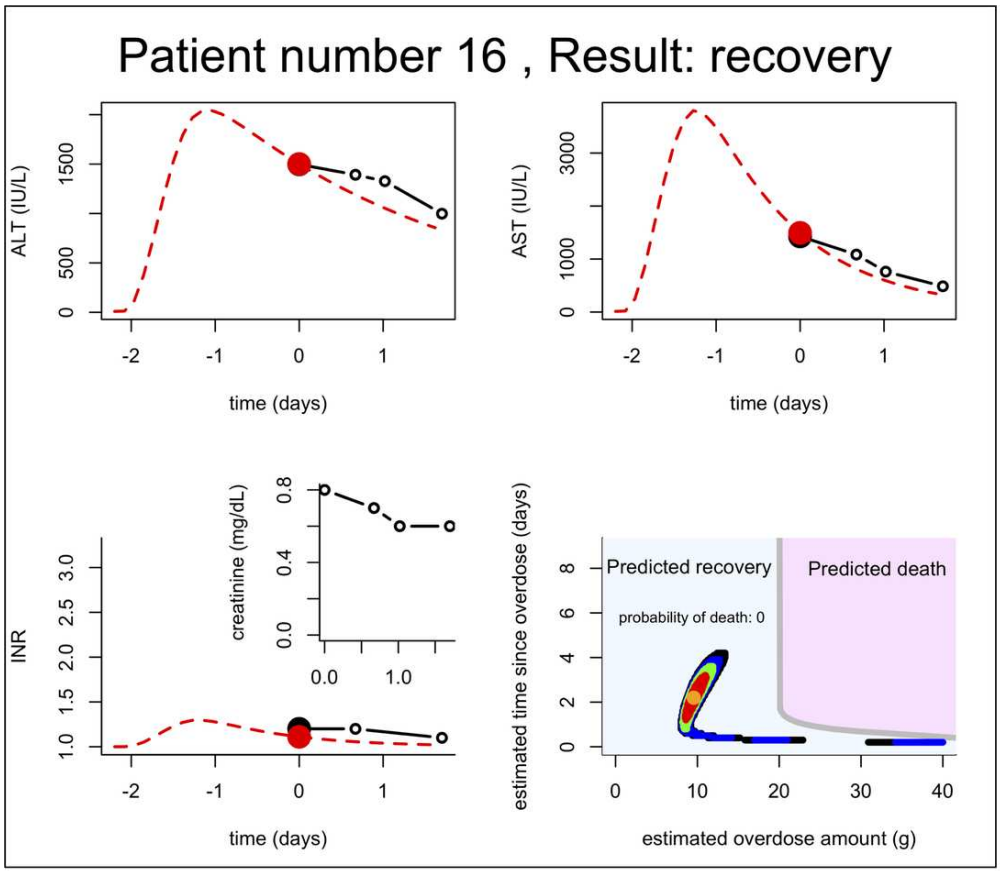
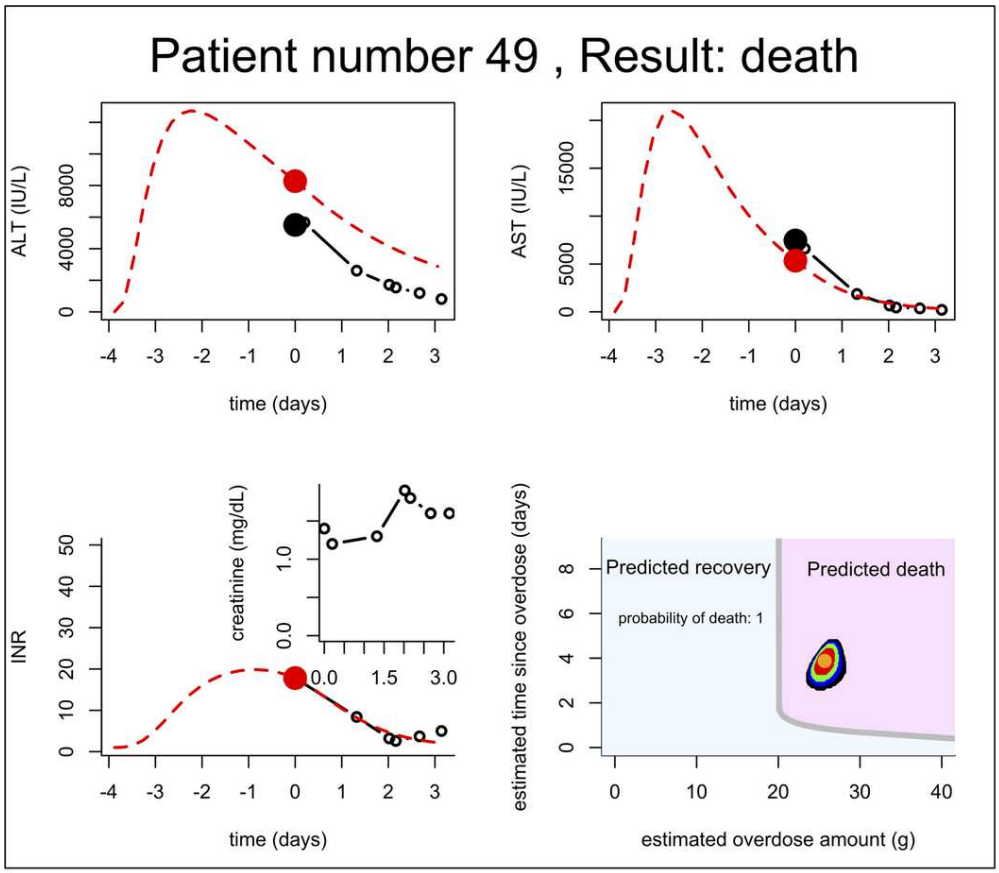



Figure 3C: Markers of liver damage (small black open circles) and model predictions (red dashed line) based on least squares fits of initial AST, ALT, and INR (large black filled circle) to modeled AST, ALT, and INR (large red filled circle) for four representative patients. Time t=0 indicates the time of admission to hospital. The estimated overdose amount and time since overdose for each patient is given by the orange dot in the lower right panel. Refer to the Supplementary Information for more detail.
46x40mm (600 x 600 DPI)




44x39mm (600 x 600 DPI)

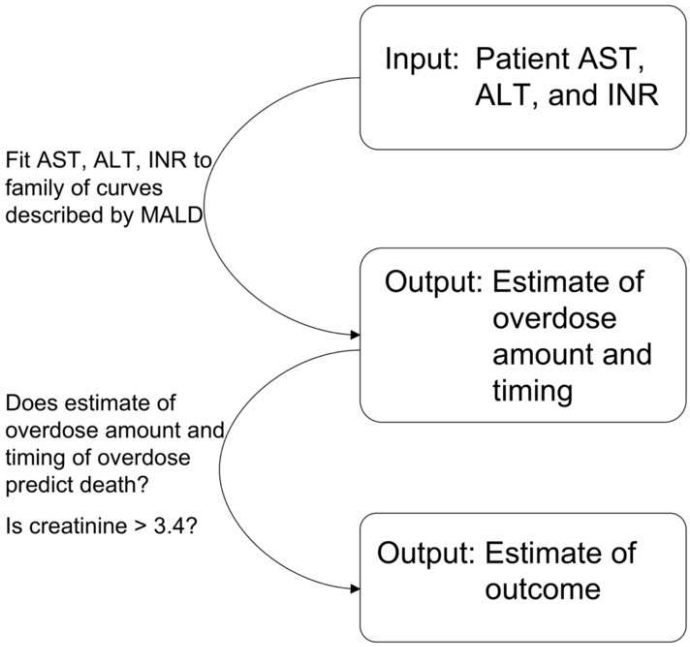



Figure 4: A schematic description of how MALD can be used to estimate overdose amount, timing and outcome. Patient AST, ALT, and INR are fit to a family of curves described by MALD to estimate overdose amount, timing, and outcome. If outcome is predicted to be poor, liver transplantation may be necessary.
43x33mm (600 x 600 DPI)